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Beck-Schimmer, Beatrice ; Schadde, Erik ; Schläpfer, M

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Complete List of Authors:	Beck-Schimmer, Beatrice; University Hospital Zurich, Institute of Anaesthesiology; University of Zurich, Institute of Physiology and Zurich Center for Integrative Human Physiology (ZIHP) Schadde, Erik; Rush University Medical Center, Department of Surgery; University of Zurich, Institute of Physiology and Zurich Center for Integrative Human Physiology (ZIHP); Cantonal Hospital Winterthur, Department of Surgery Schläpfer, Martin; University of Zurich, Institute of Physiology and Zurich Center for Integrative Human Physiology (ZIHP); University Hospital Zurich, Institute of Anaesthesiology
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Volatile anaesthetics and organ protection in kidney transplantation: finally a randomized controlled trial!

Beatrice Beck-Schimmer [1, 2, 3] , Erik Schadde [2, 4, 5] and Martin Schläpfer [1, 2]

[1] Institute of Anaesthesiology, University Hospital Zurich, Zurich, Switzerland

[2] Institute of Physiology, Zurich Center of Integrative Human Physiology, University of Zurich, Zurich, Switzerland

[3] Department of Anesthesiology, University of Illinois College of Medicine at Chicago, Chicago, USA

[4] Department of Surgery, Rush University Medical Center, Chicago, IL

[5] Department of Surgery, Cantonal Hospital Winterthur, Winterthur, Canton of Zurich, Switzerland

Corresponding author:
Beatrice Beck-Schimmer, M.D.
Institute of Anaesthesiology,
University Hospital Zurich
Raemistrasse 100
CH-8091 Zurich, Switzerland
E-mail: beatrice.beckschimmer@uzh.ch

Phone: +41 44 255-2032
Phone secretary: +41 44 255-2696

Many clinical trials have been performed to evaluate if volatile anaesthetics are protective in scenarios of ischemia-reperfusion (I/R). While the majority of studies focused on I/R injury related to cardiac surgery with the use of the cardiopulmonary bypass,[1 2] some were also performed in lung surgery with one-lung ventilation,[3] liver resections under inflow occlusion[4] as well as liver transplantation.[5] The study of Niewuwenhuijs-Moeke and her colleagues is the first trial evaluating the direct effect of volatile anaesthetics on kidneys undergoing I/R injury in the process of transplantation (Volatile Anaesthetic Protection of Renal transplants, VAPOR-1).[6] The authors of this work have to be congratulated for their efforts. So far, only *in vivo* animal experiments have been performed[7] addressing the impact of volatile anaesthetics on renal I/R injury, or else the kidneys were evaluated as a secondary outcome in clinical trials.[2] Therefore, data of this study increase the knowledge and experience within the topic of organ protection and volatile anaesthetics.

In the current study, the urinary biomarkers kidney injury marker-1 (KIM-1), N-acetyl-β-D-glucosaminidase (NAG) and heart-type fatty acid binding protein (H-FABP) were defined as primary outcome[6] to achieve a realistic sample size. At the same time the authors also evaluated clinical outcomes such as rejection rate in the two-year follow up after transplantation. In this three-arm study, donor and recipient couples were randomly assigned to a propofol group where donor and recipients were anaesthetized with propofol (PROP), a sevoflurane group using the same anaesthetic for both donor and recipient (SEVO) as well as a group with propofol anaesthesia for the donor and sevoflurane for the recipient (PROSE). The urinary markers KIM-1 and NAG were increased two days after transplantation in the SEVO group, glomerular filtration rate at three, six and 12 months were similar in all three

groups. The two-year rejection rate was significantly lower in the PROSE compared to the PROP group.

It is certainly justified to use biomarkers as surrogates for clinical outcomes in a pioneering randomized controlled trial (RCT) using a small sample size. However, the transient differences in urinary biomarker concentrations at day two in favour of propofol with increased values of KIM-1 and NAG in the SEVO remains difficult to interpret and clinical conclusions should be avoided. Taking also the dynamic of urinary accumulation of biomarkers after transplantation into account, presenting sometimes with two peaks, makes interpretation of the current results even more challenging.

A significant clinical finding of the VAPOR-1 trial, however, is the decreased rate of acute rejections in recipients after two years in the PROSE group compared to those in the PROP group.[6] This raises the question if there is indeed a prolonged effect provided by intraoperative protection of volatile anaesthetics as there are studies suggesting that the degree of I/R injury has an effect on long-term immunological outcome.[8]

It is impressive that this inaugural study could be performed in the population of living related kidney transplant recipients. However, it is important to realise that recipients of live organ donation may not represent the most vulnerable group of patients for I/R damage in transplantation. Donor organs from living donors are considered ideal with regard to function, and cold as well as warm ischemia time are generally kept as short as possible. As a consequence, injury may be as minimal as can be achieved in transplantation. Future trials should focus on scenarios of higher vulnerability such

as impaired donor organ function and/or increased warm ischemia time, as for example observed in extended criteria donor (ECD) grafts or donation after cardiac death (DCD) grafts, respectively. These kidneys may experience severe I/R injury. As a consequence, renal function is impaired and outcome is certainly less favourable.[9] Therefore protection may be more effective.

Now, what type of anaesthesia should we use for living related kidney transplantations based on the results of Niewuwenhuijs-Moeke's study? Some may be tempted to prefer propofol due the lower kidney injury markers. Reduced rejection rate long term in the sevoflurane group, however, may be clinically more relevant. Differences in secondary outcomes may certainly lead the way to further studies. For sure we need future large trials to confirm results. A lot of thought has to go into the design of such clinical studies with increasing awareness for possible confounders, that small randomized trials (RCTs) may fall prey to. Improved preservation solutions, faster technical surgery, medication such as opioids, statins and beta blockers are well known to positively influence I/R injury, others are currently being defined. Depth of anaesthesia[10] or low mean arterial pressure[11] may well be new confounders, which impact on outcome endpoints in clinical trials of perioperative care. Such parameters have to be accounted for in the design of new large RCTs via strict protocols.

It is encouraging to know that the authors of VAPOR-1 already designed a follow-up study, VAPOR-2 (ClinicalTrials.gov; NCT02727296). This large multicentre trial with more than 500 patients will compare propofol versus sevoflurane anaesthesia in recipients of living, DCD and donation after brain death (DBD) kidneys with the primary endpoint of incidence of acute rejection of the kidney allograft during one-

year follow-up. VAPOR-1 helped to define the primary endpoint of the new trial. We hope that VAPOR-2 will answer the question if sevoflurane or propofol should be used in kidney transplantation.

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